

Attorney Docket No.: UMD-0104
Inventors: Welsh et al.
Serial No.: 10/534,296
Filing Date: December 9, 2005
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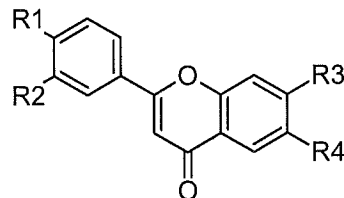
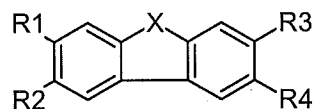
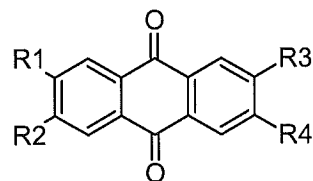
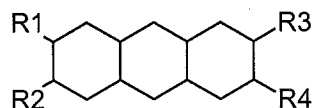
This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (original): A novel pharmacophore model as defined by the parameters of Table 4 and Table 5.

Claim 2 (original): The novel pharmacophore model of claim 1, wherein scaffold molecules derived therefrom can be used as a basis for compounds directed to inotropic Na, K-ATPase inhibition.

Claim 3 (original): The novel pharmacophore model of claim 1, wherein the model produces an Na, K-ATPase inhibitor compound of the formula:



wherein R1, R2, R3 and R4 can be any organic functional group containing a hydrogen bond donor or a hydrogen bond acceptor and X is any element or group that allows the compound to retain inotropic activity.

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Claim 4 (original): The novel pharmacophore model of claim 3, wherein X is N, O, S, or C.

Claim 5 (original): A method of using a pharmacophore model to create an Na, K-ATPase inhibitory compound comprising the steps of:

- (a) creating alignment between SERCA and Na, K-ATPase, wherein SERCA is a template;
 - (b) transferring coordinates from the template to a model for structurally conserved regions;
 - (c) generating variable regions;
 - (d) refining the model through energy minimization steps;
- and
- (e) performing docking analysis of prospective drug candidates.

Claim 6 (original): The method of claim 5, further comprising the steps of:

- (f) delineating the essential pharmacophoric elements for high binding affinity;
- (g) searching databases of known compounds using the restraints as implicated by the pharmacophore with allowable tolerances; and
- (h) utilizing de novo rational drug design and computer aided molecular modeling to design novel compounds using the restraints as implicated by the pharmacophore with allowable tolerances.

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Claim 7 (original): The method of claim 6, wherein the allowable tolerances in steps (g) and (h) is $\pm 10\%$.

Claim 8 (original): The method of claim 5, wherein step (a) is comprised of dynamic programming and threading.

Claim 9 (original): The method of claim 5, wherein SERCA is SERCA1a.

Claim 10 (original): The method of claim 5, wherein the steps are carried out using a computer-readable medium having computer-executable instructions.

Claim 11 (original): The method of claim 10, wherein the steps are carried out using molecular modeling software.

Claim 12 (original): A method of treating an individual with a heart disease comprising administering a therapeutically effective amount of an novel inotropic compound created using a novel pharmacophore model as defined by Table 4 and Table 5.

Claim 13 (original): The method of claim 12, wherein the novel pharmacophore model produces novel inotropic drugs of the formula of:

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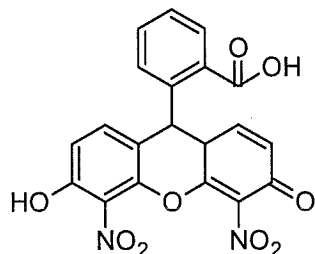
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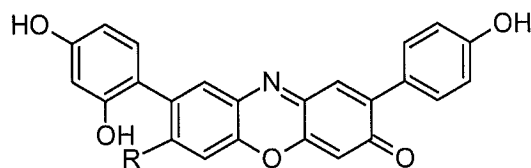
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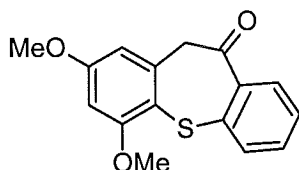


4',5' Dinitroflorescein

or



#19 R= NH₂ or OH



Claim 14 (original): The method of claim 13, wherein the novel drugs have a wider therapeutic index than either ouabain or digoxin.

Claim 15 (original): The method of claim 12, wherein the heart disease treated is congestive heart failure and supraventricular arrhythmia.

Claim 16 (original): The method of claim 12, wherein the novel inotropic compound is administered in a pharmaceutically acceptable carrier.

Claim 17 (original): The method of claim 12, wherein the novel inotropic compound is administered parenterally or orally.

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Claim 18 (original): The method of claim 12, wherein residues Q111, D121, E908 and M973 are unaltered.